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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/369,941	KENSIL, CHARLOTTE A.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4-8-04, 4-26-04 and 5-19-04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21-28,63-78,90,92-103,105-114 and 117-149* is/are pending in the application.

4a) Of the above claim(s) *122-125 and 135-149* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21-28,63-78,90,92-103,105-114,117-121 and 126-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-26-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The after final amendment filed 4-8-04 has been entered as requested in the paper filed 5-19-04. The amendment filed 4-26-04 has been entered as requested in the request for continued examination filed 4-26-04.

Applicant's arguments filed therein have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 117-126 were added in the amendment filed 4-8-04. Claims 127-149 were added in the amendment filed 4-26-04. Claims 19, 21-28, 63-78, 90, 92-103 and 105-114 and 117-149 are pending.

Election/Restrictions

Newly submitted claims 122-125 and 135-149 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 122-125, 135-142, 145, 148 and 149 require an antigen. The claims are only under consideration as they relate to nucleic acid sequences encoding an antigen. Claims 143 and 144 are directed toward a use, which cannot examined because they are so unclear because they do not recite any steps. The use is for manufacture of a vaccine, which is patentably distinct from the claims under consideration because

different steps would be required. Claims 146-149, directed toward a method of making a product by combining CpG and saponin, are also patentably distinct from the claims under consideration because different steps would be required. The burden required to search the steps of making with the product and the steps of using the product to induce an immune response would be undue. The burden required to examine methods of making with products and methods of using would be undue (see the length of this office action).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 122-125 and 135-149 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 19, 21-28, 63-78, 90, 92-103, 105-114, 117-121 and 126-134 are under consideration in the instant office action as they relate to a composition comprising a) saponin and b) an immunostimulatory oligonucleotide, and to a method of using such a composition (Group II). The claims are not being examined as they relate to a composition comprising a) saponin, b) an immunostimulatory oligonucleotide, and c) an antigen, or methods of using such a composition.. For examination purposes a "nucleic acid sequence encoding an antigen" is not an antigen because antigens are proteins, and because nucleic acid sequences are materially distinct and separate than proteins.

Claim Objections

The term "groups" in claims 25, 65, 66, 96, 97, 110 should be –group--.

Claims 64, 67, 68, 70, 72, 74, 76 and 90 should be limited to – 1) administering the immune adjuvant composition of claim 63 to the individual; and 2) administering a nucleic acid molecule comprising a nucleotide sequence encoding the antigen to the individual... -- to be clearer. It is noted that the claims written this way would still encompass administering the immune adjuvant and the nucleic acid molecule together or separately. The phrase "wherein the nucleic acid molecule... or in the same formulation with the immune adjuvant composition" is not needed.

If the phrase is left in, the phrase "in the same formulation" in claims 64, 67, 68, 70, 72, 74, 76, 90 should be –together-- to parallel the term "separately" and the language used in the claims.

In claim 120, the phrase "is selected from the group comprising:" should be – selected from the group consisting of-- to be in proper Markush format.

In claims 121, 126, 131 and 134, the Markush group is not in proper format because "or" is used. The species within the genus should be clear. For example, the phrase "selected from the group consisting of Quil-A, QS21, QS7 and QS17" in claim 131 would be clear and in proper Markush format.

Claims 121, 126 and 134 are also unclear because a "solution" is equivalent to a "suspension" and an "elixir", because a "liquid solution" is redundant, because a "sterile

liquid or solution" is a species within the species of "liquid or solution", because a suspension or elixir for oral administration" is a species within the species of "liquid or solution" and because the species within the Markush Group use "or". Please clearly set forth the structure of carrier in the Markush Group in claims 121 and 134 (e.g. wherein the carrier is a capsule or a liquid).

Claim 133 is not in proper Markush format because it does not have an –and- separating the species and uses "comprising". The phrase "selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:1" is in proper Markush format.

Claim Rejections - 35 USC 112

I. Claims 64, 67, 68, 70, 72, 74, 76, 90, 92-103, 105-114, 127 and 128 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection of "derived" (19, 63, 65, 69, 71, 73, 75, 103) has been withdrawn because claim 2 as originally filed was drawn to a vaccine comprising an antigen, a saponin adjuvant and an immunostimulatory oligonucleotide, wherein the saponin adjuvant is derived from Quillaja saponaria.

The rejection of claims 25, 65, 66, 96, 97 and 110 regarding "phosphate-modified nucleotides" under new matter has been withdrawn because the phrase has been amended.

The rejection of claims 64, 67, 68, 70, 72, 74, 76, 80, 90 and 103 regarding administering a nucleic acid sequence encoding an antigen to an individual under new matter has been withdrawn in view of the amendment to the claims. However, the amendment to claims 64, 67, 68, 70, 72, 74, 76 and 90 has raised a new rejection under new matter.

Claims 64, 67, 68, 70, 72, 74, 76, 90, 103 and 127 are rejected under new matter because the specification does not support administering 1) a saponin and an immunostimulatory oligonucleotide; and 2) a nucleic acid molecule encoding an antigen. Pg 10, lines 10-12 describes "immune adjuvant" but does not describe administering nucleic acids, specifically administering nucleic acids separately from the immune adjuvant. Nor does pg 10, lines 10-12, refer to the combination of saponin QS-7, QS-17 or QS-18 with an oligo with at least one unmethylated CpG dinucleotide as required claim 64. pg 12, lines 8-12, refer to increasing an immune response to antigen by administering a saponin adjuvant and an oligo. Pg 12, lines 8-12, does not describe administering nucleic acids, specifically administering nucleic acids encoding antigens, more specifically administering nucleic acids encoding antigens separately from the immune adjuvant. Pg 14, line 22, to pg 15, line 2, describes target antigens, "antigens

suitable for the enhanced immune response" (pg 14, line 17). Pg 14, line 22, to pg 15, line 2, states the antigen may include a nucleic acid encoding the antigenic protein or peptide of interest (pg 15, lines 1-2), but pg 14, line 22, to pg 15, line 2, does not describe administering nucleic acids to patients, specifically administering nucleic acids encoding antigens to patients, more specifically administering nucleic acids encoding antigens to patients separately from the immune adjuvant. The paragraph bridging pg 14-15 merely states the "antigens suitable for the enhanced immune response" may be "a protein, a peptide, a polysaccharide, a lipid, a glycolipid, a phospholipid, or a nucleic acid encoding the antigenic protein or peptide of interest." Pg 16, lines 12-15, describe stimulating immunity to an antigen by administering a vaccine comprising an antigen, a saponin adjuvant and an immunostimulatory oligo. Pg 16, lines 12-15, does not describe administering a nucleic acid encoding the antigen. It is not readily apparent that the antigen administered to a patient on pg 16, lines 12-15, refers to the nucleic acid sequence encoding an antigen described on pg 15, lines 1-2, because the paragraph bridging pg 14-15 is describing antigens suitable for the enhanced immune response and does not describe administering a nucleic acid encoding an antigen to a patient. Pg 18, lines 9-11, describes administering a composition "as a single injection of a mixed formulation of saponin, oligonucleotide, and antigen or as separate injections given at the same site with a short period of time" but does not describe administering nucleic acids, specifically administering nucleic acids encoding antigens.

Therefore, it is not readily apparent that applicants contemplated administering a nucleic acid sequence encoding an antigen because the antigen in the paragraph bridging pg 14-15 refers to the antigen "suitable for the enhanced immune response" and is not limited the antigen used in the composition on pg 16, lines 12-15, or pg 18, lines 9-11. Nor is it readily apparent that applicants contemplated administering a nucleic acid sequence encoding an antigen together with or separately from administering a saponin and immunostimulatory oligonucleotide as claimed.

Applicants argue the specification does not have to disclose *ipsis verbis* what is being claimed. Rather, applicants argue, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question. In addition, applicants argue the "specification explicitly teaches, and thus does support, the administration of a nucleic acid encoding an antigen" (pg 17 of response filed 4-26-04).

Applicants' arguments are not persuasive. Applicants did not reasonably convey to persons of skill in the art that the inventors had considered administering a nucleic acid sequence encoding the antigen to an individual. At best, the specification suggests the antigens suitable for enhanced immune response may be a nucleic acid sequence encoding the antigen (¶ bridging pg 14-15). The specification teaches administering the antigen to an individual (pg 16, lines 12-15; pg 18, lines 9-11) but does not suggest administering the nucleic acid encoding the antigen. As written in the paragraph

bridging pg 14-15, it appears that the antigens "suitable for enhanced immune response" are merely target antigens because the specification describes using saponin and immunostimulatory oligonucleotides alone to enhance the immune response against antigens (pg 2; pg 3, lines 4-10; pg 13, last 4 lines). It is not readily apparent that the antigens "suitable for the enhanced immune response" on pg 14-15 are part of any composition or are being delivered to individuals.

In addition, applicants' argument that the "specification explicitly teaches, and thus does support, the administration of a nucleic acid encoding an antigen" is flawed. The argument is based on pg 12, lines 8-12, pg 16, lines 12-15, pg 18, lines 9-11, which are discussed above and do not teach administering a nucleic acid sequence encoding an antigen to an individual (see paragraph above for a description of what is taught in each citation). The term "explicit" is defined as "precisely revealed or expressed without vagueness, implication, or ambiguity" (see definition of "explicit" from Merriam-Webster Online dictionary). Therefore, applicants' argument misuses the term "explicit" because nowhere does the specification clearly discuss administering a nucleic acid sequence encoding an antigen. Piecing together three parts of the specification would, at best, be an "implicit" description of administering a nucleic acid sequence encoding an antigen to an individual; however, such an argument would not be found persuasive for reasons in the paragraph above.

Claim 113 remains rejected and new claim 127 is rejected because the phrase "wherein the nucleic acid comprising a nucleotide sequence encoding the antigen is administered to the individual within 2 days of said administering of the immune adjuvant" remains new matter. Pg 18, line 9, contemplates administering the composition as a "single injection of a mixed formulation of saponin, oligonucleotide, and antigen or as separate injections given at the same site within a short period of time (i.e. 0-2 days)." The specification does not contemplate administering a nucleic acid sequence encoding an antigen and a mixture of saponin and immunostimulatory oligonucleotide for reasons cited above. In addition, one of skill cannot extrapolate administering A and B+C separately as claimed from the description on pg 18, line 9, which appears to be limited to delivering A+B+C together or delivering A, B and C "as separate injections", i.e. each one by themselves.

Applicants argue the specification reasonably conveys to those of skill that applicants had possession of the species claimed (i.e. administering A and B+C separately within 0-2 days, pg 18 of response filed 4-26-04). Applicants argue only four possible combinations exist in the description on pg 18, lines 9-11, and that one of skill would have reasonably concluded that applicants had considered all four combinations including the one claimed. Applicants' argument is flawed. First, pg 18, lines 9-11, appears to be limited to delivering A+B+C together, or delivering A, B and C "as

separate injections". Second, using applicants' logic, there are at least 13 possible combinations from the description on pg 18, lines 9-11:

ABC together

A+BC

A+B+C

A+C+B

AB+C

AC+B

B+AC

B+A+C

B+C+A

BC+A

C+AB

C+A+B and

C+B+A.

Third, using applicants' logic taken with applicants' argument that "antigen" encompasses any of the 7 compounds in the sentence bridging pg 14-15 other than DNA encoding antigen, the number of combinations is exponentially greater than 13. Therefore, it would not be readily apparent to one of skill in the art that applicants had

considered the specific combination of administering a nucleotide sequence encoding an antigen within 2 days of administering CpG plus saponin as claimed.

II. Claims 121, 126, 131 and 134 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The rejection of claims 64, 67, 68, 70, 72, 74, 76 and 90 as being unclear has been withdrawn in view of the amendments to the claims.

The rejection of claims 64, 67, 68, 70, 72, 74, 76 and 90 regarding the phrase "inducing the immune response in an individual to an antigen" has been withdrawn in view of the amendments to the claims.

The rejection of claims 75 and 77 regarding "a chemically modified saponin" has been withdrawn. "Chemical modification" is defined as "alteration in the structure of a molecule, typically a macromolecule such as a protein, by chemical means; often, the covalent addition by some reagent" (see Stedman's Medical Dictionary definition of "chemical modification" enclosed). The specification and the art at the time of filing taught purifying saponins such as QS-21 from a crude extract of saponin (pg 1, lines 10-14, of specification; Chavali, 1987, Int. J. Immunopharmac. Vol. 9, pg 675-683; see pg 676, col. 1, "Saponins"). However, the process of purifying saponins does not appear to alter the structure of the saponin molecules within the crude extract. Therefore, it would

be readily apparent to those of skill in the art that "a chemically modified saponin" has an alteration in the structure of the saponin molecule by chemical means.

The rejection of claims 24, 28, 95, 99, 108 and 112 regarding "motif" has been withdrawn because the term has been deleted.

The rejection of claims 27, 98 and 11 regarding "motif" has been withdrawn in view of applicants arguments filed 4-26-04, pg 21.

Regarding claims 121, 126, 131 and 134, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC 102

The rejection of claims 75, 76, 113 and 114 under 35 U.S.C. 102(e) as being anticipated by Urban (6,013,258, Jan 11, 2000) as supported by Krieg (Trends in Microbiology, Jan. 1, 1998, Vol. 6, pages 23-26) has been withdrawn because Urban did not teach using a chemically modified saponin as claimed. Quil A taught by Urban was not chemically modified saponin because it was purified from *Quillaja saponaria* and because the structure of Quil A was not altered during the process of purification by chemical means (see Stedman's Medical Dictionary definition of "chemical modification").

The rejection of claims 75, 76, 113 and 114 under 35 U.S.C. 102(e) as being anticipated by Sasaki (US Patent 5,808,024, Sept. 15, 1998) as supported by Krieg (Trends in Microbiology, Jan. 1, 1998, Vol. 6, pg 23-26) has been withdrawn because Urban did not teach using a chemically modified saponin as claimed. QS21 taught by Sasaki was not chemically modified saponin because it was purified from *Quillaja saponaria* and because the structure of QS21 was not altered during the process of purification by chemical means (see Stedman's Medical Dictionary definition of "chemical modification").

Claim Rejections - 35 USC 103

III. Claims 19, 21-27, 63-68, 73-77, 90, 95-98, 100-102, 113 and 114 remain rejected and claims 117-121 and 126-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner (Sept. 1997, PNAS, Vol. 94, pages 10833-10837) in view of Kensil (1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pages 1-55).

Weiner taught administering phosphorothioated oligonucleotide 1643 increased the humoral immune response in a mouse (page 10834, col. 1). 1643 has three unmethylated CpG motifs (pg 10834, Table 1; note the "ACGC" "TCGA" and "TCGA" = claim 27; pg 10833, col. 2, 11 lines from the bottom). Weiner did not teach combining 1643 with QS-7, -17, -18 or -21. However, at the time of filing, Kensil taught combining

QS-7, -17, -18 or -21 with vaccines for an adjuvant effect (pg 23) and with other adjuvants to increase the adjuvant effect (pg 6, 2nd full ¶).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotide 1643 of Weiner with QS-7, -17, -18 or -21 as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Weiner and Kensil are directed toward compositions with adjuvants that increased the humoral immune response and 2) 1643 and QS-7, -17, -18 or -21 could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the humoral immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to combine oligonucleotide 1643 and QS-7, -17, -18 or -21 to increase the humoral immune response.

Applicants' arguments are addressed below.

IV. Claims 19, 21, 24, 25, 27, 28, 65, 67, 69, 70, 73-77, 90, 95-98, 100-102, 113 and 114 remain rejected and claims 117-121 and 126-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner (Sept. 1997, PNAS, Vol. 94, pg 10833-10837) in view of Kensil (1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pg 1-55).

Weiner taught administering oligonucleotide 1758 increased the humoral immune response in a mouse (pg 10834, col. 1) that has unmethylated CpG motifs and is equivalent to SEQ ID NO:1. 1758 is phosphorothioated (pg 10833, col. 2, 11 lines from the bottom) (claims 25, 26, 55, 56 and 65-68). Weiner did not teach combining 1758 with Quil A. However, at the time of filing, Kensil taught combining Quil A with other adjuvants to increase the adjuvant effect (pg 6 and pg 23). Quil A is purified from *Quillaja saponaria,* is less purified than QS-7, 17, 18 or -21 and has less of an adjuvant effect than QS-7, 17, 18 or -21 (page 3, 5, 11 and Fig. 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotide 1758 of Weiner with Quil A as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Weiner and Kensil are directed toward compositions with adjuvants that increase the immune response and 2) 1758 and Quil A could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to combine oligonucleotide 1758 and Quil A to increase the immune response.

Applicants' arguments are addressed below.

V. Claims 19, 21-27, 63-68, 71-78, 90, 95-98, 100-102, 113 and 114 remain rejected and claims 117-121 and 126-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chu (Nov. 17, 1997, J. Exp. Med., Vol. 186, pg 1623-1631) in view of Kensil (Kensil, 1996, Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 13, No. 1 and 2, pg 1-55) for reasons of record.

The effective filing date for administering 1826 (SEQ ID NO:2) with saponin as claimed is 4-8-99, the filing date of provisional application 60/128,608. Provisional application 60/095,913, filed 8-10-98, did not teach any synergy betweenChu taught administering oligonucleotide 1826 or 1760 as an adjuvant increased the IgG2a immune response in a mouse (pg 1625, col. 2, Fig. 1A and 1D). 1826 and 1760 have unmethylated CpG motifs, and 1826 is equivalent to SEQ ID NO:2. 1826 and 1760 are phosphorothioated (page 1625, col. 1, Table 1). Chu did not teach combining 1826 or 1760 with Quil A, QS-7, -17, -18 or -21. However, Kensil taught combining Quil A, QS-7, -17, -18 or -21 with other adjuvants to increase the adjuvant effect (page 6, line and page 23). Quil A is purified from *Quillaja saponaria,* and QS-7, 17, 18 and -21 are purified from a less pure formulation of saponin. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotides 1826 or 1760 of Chu with Quil A, QS-7, 17, 18 or -21 as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Chu and Kensil are directed toward compositions with adjuvants

that increase the immune response and 2) 1826 or 1760 and Quil A, QS-7, 17, 18 or -21 could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to add oligonucleotide 1826 or 1760 and Quil A, QS-7, 17, 18 or -21 to increase the IgG2a immune response.

Applicants' arguments are addressed below.

Applicants argue the specification and Friede (WO 00/62800) show unexpected synergy between "saponins with immune adjuvant activity... ...derived from *Quillaja saponaria*" and "an immunostimulatory oligonucleotide comprising at least one unmethylated CpG". Applicants argue the species of unexpected results shown in the specification and in Friede represents the genus of saponins and unmethylated CpGs claimed. Applicants' argument is not persuasive.

1) Example 1 (pg 20) and Figure 1 of the instant application describe using 1758 (SEQ ID NO:1) described by Weiner and used as the basis of rejection IV.

In Figure 1, assuming the data at the Effector:target ratio of 25 from top to bottom are:

1.25 ug QS-21 + 50 ug phosphorothioated CpG 1758 = 85,

10 ug QS-21 + 50 ug phosphorothioated CpG 1758 = 81,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 80,

10 ug QS-21 = 74

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 34

50 ug phosphorothioated CpG 1758 = 4

10 ug phosphorothioated CpG 1758 = 0

1.25 ug QS-21 = 0,

using the values for QS-21 or 1758 alone the expected values would be:

1.25 ug QS-21 + 10 ug 1758 = 0 + 0

1.25 ug QS-21 + 50 ug 1758 = 0 + 4

10 ug QS-21 + 10 ug 1758 = 74 + 0

10 ug QS-21 + 50 ug 1758 = 74 + 4

The unexpected results are:

1.25 ug QS-21 + 10 ug 1758 because 34 is greater than 0 + 0; and

1.25 ug QS-21 + 50 ug 1758 because 85 is greater than 0 + 4.

10 ug QS-21 + 10 ug 1758 is an expected result because 80 is not significantly different than 74 + 0 statistically; and

10 ug QS-21 + 50 ug 1758 is an expected result because 81 is not significantly different than 74 + 4 statistically.

Unexpected results in Example 1, Fig. 1 of the instant application do not represent the genus of saponin and CpG oligonucleotide claimed because some species within the genus cause expected results.

2) Example 4 (pg 22-23) and Figure 5 of the instant application describe using 1826 (SEQ ID NO:2) described by Chu and used as the basis of rejection V.

In Figure 5, assuming

1.25 ug QS-21 = 52,

10 ug QS-21 = 93,

10 ug 1826 = 87,

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1826 = 46,

10 ug QS-21 + 10 ug phosphorothioated CpG 1826 = 986,

using the values for QS-21 or 1826 alone the expected values would be:

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1826 = 52 + 87,

10 ug QS-21 + 10 ug phosphorothioated CpG 1826 = 93 + 87.

The unexpected result is:

10 ug QS-21 + 10 ug phosphorothioated 1826 because 986 is greater than 93 + 87.

1.25 ug QS-21 + 10 ug phosphorothioated 1826 shows antagonistic result because 46 less than the expected value (52 + 87).

The unexpected results in Example 4, Fig. 5 for the species of 10 ug QS-21 + 10 ug phosphorothioated 1826 in the instant application do not correlate to the entire genus of saponin and CpG oligonucleotide claimed because Fig. 5 shows another species within the genus claimed that caused an antagonistic effect. The limited unexpected value obtained in Example 4 is not representative of the genus claimed.

3) Example 1 (pg 23-25) of Friede (WO 00/62800) appears to describe using 1826 (SEQ ID NO:2) described by Chu and used as the basis of rejection V) because Friede refers to the 1826 by Krieg. Krieg taught 1826 CpG was phosphorothioated.

In Fig. 1, assuming

20 ug 1826 = 750,

5 ug QS21 = 1250, and

20 ug 1826 + 5 ug QS-21 = 2200,

using the values for QS-21 or 1826 alone the expected values would be:

20 ug 1826 + 5 ug QS21 = 750 + 1250,

No unexpected results were obtained in Fig. 1 of Friede. The obtained result of 2200 was expected because 2200 is not significantly greater than 750 + 1250 statistically. Therefore, Fig. 1 of Friede does not support the argument of unexpected results.

b) In Example 1, Fig. 2, of Friede assuming

20 ug 1826 = 120,

5 ug QS21 = 180, and

20 ug 1826 + 5 ug QS-21 = 490,

using the values for QS-21 or 1826 alone the expected values would be:

20 ug 1826 + 5 ug QS21 = 120 + 180,

The obtained result of 490 was an unexpected result because 490 is greater than 120 + 180.

While Figure 2 of Friede shows unexpected results for the species of phosphorothioated 1826 and QS21 within the genus claimed, the . The results in Example 1, Fig. 2 of Friede do not represent the genus of saponin and CpG oligonucleotide claimed because some species within the genus cause expected or antagonistic results as shown in Fig. 1 of Friede and Fig. 1 and 5 of the instant application.

4) Example 2 (pg 25-27) of Friede (WO 00/62800):

Fig. 3 shows unexpected results were obtained using 50 ug 2006 and 4.5 ug QS-21.

Fig. 4 shows two unexpected results were obtained using 50 ug 2006 and 4.5 ug QS-21 when A/Beijing and B/Panama were the targets and one expected result when A/Johann was the target (because the expected result (50 + 180) is not significantly greater than the obtained result (250)).

The tally:

9 unexpected results, 4 expected results and 1 antagonistic result.

Applicants have not taken into consideration the other Figures in the instant application.

5) Example 2 (pg 21) and Figure 2 of the instant application:

In Figure 2, assuming the values at the Effector:target ratio of 25 are:

No adj = 0,

2 ug CpG = 0,

10 ug CpG = 0,

50 ug CpG = 61,

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 0,

1.25 ug QS-21 + 50 ug phosphorothioated CpG 1758 = 42,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 62,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 30,

1.25 ug QS-21 = 0, and

10 ug QS-21 = 36,

the expected values would be:

1.25 ug QS-21 + 10 ug 1758 = 0 + 0

1.25 ug QS-21 + 50 ug 1758 = 0 + 61

10 ug QS-21 + 10 ug 1758 = 36 + 0

10 ug QS-21 + 50 ug 1758 = 36 + 61

The unexpected result is:

10 ug QS-21 + 10 ug 1758 because 62 is greater than 36 + 0.

1.25 ug QS-21 + 10 ug 1758 is an expected result because 0 is not significantly different than 0 + 0 statistically

1.25 ug QS-21 + 50 ug 1758 is an antagonistic result because 42 is less than the expected 0 + 61; and

10 ug QS-21 + 50 ug 1758 is an antagonistic result because 30 is less than the expected 36 + 61.

6) Example 3 (pg 21) and Figure 3 of the instant application:

In Figure 3, assuming the values of IgG1 are:

10 ug CpG = 1000

50 ug CpG = 1000

1.25 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 5000,

1.25 ug QS-21 + 50 ug phosphorothioated CpG 1758 = 20,000,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 110,000,

10 ug QS-21 + 10 ug phosphorothioated CpG 1758 = 100,000,

1.25 ug QS-21 = 1000, and

10 ug QS-21 = 100,000,

the expected values would be:

1.25 ug QS-21 + 10 ug 1758 = 1000 + 1000

1.25 ug QS-21 + 50 ug 1758 = 1000 + 1000

10 ug QS-21 + 10 ug 1758 = 100,000 + 1000

10 ug QS-21 + 50 ug 1758 = 100,000 + 1000

The unexpected results are:

1.25 ug QS-21 + 10 ug 1758 because 5000 is greater than 1000 + 1000.

1.25 ug QS-21 + 50 ug 1758 because 20,000 is greater than 1000 + 1000.

10 ug QS-21 + 10 ug 1758 is an expected result because 110,000 is the expected value.

10 ug QS-21 + 50 ug 1758 is an expected result because 100,000 is not significantly different than the expected 100,000 + 1000 statistically.

7) Antagonistic results were obtained in Fig. 4 of the instant application because 1.25 ug QS-21 + 10 ug CpG caused an IgG titer of 74 which is much less than the expected 40+63. Fig. 4 showed unexpected results with 10 ug QS-21 + 10 ug CpG.

8) Antagonistic results were obtained in Fig. 6 of the instant application because 1.25 ug QS-21 + 10 ug CpG caused an IgG titer of 76 which is less than the expected 12+71. Fig. 6 showed unexpected results with 10 ug QS-21 + 10 ug CpG.

9) Unexpected results were obtained in Fig. 7 of the instant application. 1.25 ug QS-21 + 10 ug CpG caused an IgG titer of 785 which is greater than the expected 14 + 19. 10 ug QS-21 + 10 ug CpG caused an IgG titer of 8454 which is greater than the expected 186 + 19.

10) Antagonistic results were obtained in Fig 8 of the instant application because 1.25 ug QS-21 + 10 ug CpG caused an IgG titer of 239 which is much less than the expected 5+352. 10 ug QS-21 + 10 ug CpG caused an unexpected IgG titer of 44806 which is greater than the expected 94 + 352.

The tally in the specification:

13 unexpected results, 5 expected results and 6 antagonistic results.

The tally in the specification plus what was known in the art at the time of filing:

(this includes Friede Example 1, Fig. 1 and 2, which used oligonucleotide 1826 known in the art):

14 unexpected results, 6 expected results and 6 antagonistic results.

The tally in the specification plus what was known and unknown in the art at the time of filing within the genus claimed:

(this adds Friede Example 2, Fig. 3 and 4, which used oligonucleotide 2006 which was not described in the art at the time of filing):

19 unexpected results, 6 expected results and 7 antagonistic results.

No matter how one of skill would look at the data in the specification and Friede, the examples of saponin plus CpG that provided unexpected results are not representative of the genus claimed. The limited examples of unexpected synergy in the instant application and Friede cited by Dr. Kensil in the declaration in paragraph 5 do not support unexpected synergy for the genus claimed because many combinations within the genus only provided expected results and some provided less than expected results.

Furthermore, the data in Example 2 of Friede cannot be relied upon for post-filing evidence of synergy because the specification does not provide adequate written description for CpG 2006. Applicants argue post-filing evidence can be used to show unexpected properties of an invention and cites Ex Parte LADD, 112 USPQ 337 (PTO Board of Appeals 1955). Applicants' argument is flawed. While post-filing evidence can be used to show unexpected properties of an invention, Ex Parte LADD states that "as long as the appellants have disclosed the compound and its utility they may establish by

means of data obtained subsequent to the filing of the present application that it possesses unobvious properties as compared to the compounds of the prior art". The CpG oligonucleotide 2006 relied upon in applicants' argument of unexpected results (Friede, Example 2, pg 25, Fig. 3 and 4) was not adequately described in the specification at the time of filing or in the art at the time of filing. Therefore, applicants have not "disclosed the compound" as required by Ex Parte LADD. Despite the fact that CpG 2006 is within the genus claimed, applicants' cannot present post-filing evidence with CpG 2006 in Example 2, Fig. 3 and 4 of Friede because applicants did not adequate describe CpG 2006. It is not readily apparent that applicants had considered or possessed CpG 2006. In conclusion, the tally of unexpected, expected and antagonistic results must be limited to only the species that have adequate written description in specification plus those known in the art at the time of filing and must exclude Example 2, Fig. 3 and 4 of Friede: 14 unexpected results, 6 expected results and 6 antagonistic results.

Applicants point to paragraph 6 of the declaration by Dr. Kensil, who states CpGs are expected to act in the same manner with respect to immune adjuvant activity. Applicants' argument is not persuasive. Fig. 3 and 4 of the instant application show two different CpGs (1758 and 1826) at 10 ug provide different IgG1 titers (1000 vs 63). In the case of 1758, 10 ug caused less antibody production than no adjuvant. Thus, one of ordinary skill would not conclude that all CpGs cause the same immune response

and would not have been able to determine which CpG had an adjuvant effect or at what concentration such CpGs would provide synergy when combined with a saponin as claimed. Applicants' arguments regarding mechanism of action by which CpG "exert their activity through the same receptor" in paragraph 6 of the declaration and in the paragraph bridging pg 24-25 of the response filed 4-26-04 are moot because the specification shows 1758 caused did not stimulate the immune response as compared to no adjuvant.

Applicants point to case law from In the Matter of the Application of Kollman, 595 F.2d48(C.C.P.A. 1979) in which "the unobviousness of a broader claimed range can, in certain instances, be proven by a narrower range of data" and that "one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof." Applicants' argument is not persuasive. In this case, the data clearly shows that one of ordinary skill would not have concluded that random examples of unexpected synergy within the genus of CpG and QS saponins as claimed were representative of the genus. One of skill would have recognized that many species within the genus claimed had an antagonistic or expected effect and would have concluded that synergy would be obtained only sometimes, and that it could not be determined when synergy would occur.

Applicants argue QS saponins share structural similarities and that QS saponins in general are expected to exhibit a common immune adjuvant function (¶ 7-10 of the

declaration and ¶ bridging pg 24-25 of the response filed 4-26-04). First, Dr. Kensil shows how QS-17, -18 and –21 share two structural features (¶ 8) and that other saponins share structural similarities (¶ 9). Dr. Kensil concludes that "[b]ecause of the structural similarity of the QS saponins and the correlation of structure with function, and the evidence that QS saponin QS-21 exhibits synergy in immune adjuvant activity with CpG oligonucleotides, I conclude that synergy in immune adjuvant activity is reasonable expected to be a general property of the genus of QS saponins" (¶ 11). Applicants' argument is not persuasive.

First, the conclusion in ¶ 11 of the declaration is flawed because applicants shown no functional similarity between QS-17, -18 and –21. No "correlation of structure with function" had been established for QS-17, -18 and –21 in the art at the time of filing or by applicants, especially in view of the varying data in Fig. 1-9 of the instant application. Second, Fig. 3 of the instant application shows 1.25 ug of QS-21 did not have an adjuvant activity, but 10 ug QS-21 did have adjuvant activity. Fig. 2 of the instant application shows 1.25 ug QS-21 and 10 ug QS-21 did not have an immunostimulatory effect. one of ordinary skill in the art would easily recognize that QS-21 does not always provide an immunostimulatory effect. Given applicants' data, one of ordinary skill would conclude that QS-21 provided an immunostimulatory effect only for certain immune responses and only at certain concentrations. One of ordinary skill could not reasonably conclude that QS-21 would exhibit synergy in any immune

activity as concluded by Dr. Kensil. Nor would one of ordinary skill have been able to predict when such synergy would occur. Therefore, the variable results in the specification and Friede when using QS-21 do not adequately correlate to any other saponins as claimed.

Applicants point to Application of Katzschmann, 347 F.2d 620 (CCPA 1965) which states, "[w]e do not think it was the intent of section 103 that either the examiner, the board or this court should substitute their own speculations for the factual knowledge of those skill in the art." In this case, the examiner has supported his position (that the examples of unexpected synergy in Fig. 1 and 5 of the instant application and Friede described in paragraph 5 of the declaration are not representative of the genus claimed) with applicants' own teachings. The examiner has used data and logic, not speculation, to support his position.

Double Patenting

Claim 126 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 121. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The structure and function of the adjuvant compositions in claims 121 and 126 is identical because both require QS21, an

immunostimulatory oligonucleotide containing an unmethylated CpG dinucleotide, and a "capsule, liquid solution... ...or suspension."

The limitation of a CpG motif having the formula 5'X_1CG$X_2$3' in claim 27, 98, 111, 119 and 132 still cannot be searched because the nucleic acid is so small and may be part of any plasmid, which is very large in comparison, and cannot be adequately searched on computer databases or by eye.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

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PRIMARY EXAMINER